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THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT Application of
Muller

Group Art Unit: 1615

App'n Ser. No. 09/915,549

Examiner: Humera N. Sheikh

Filed: July 27, 2001

For: DISPERSIONS FOR THE FORMULATION OF SLIGHTLY OR POORLY
SOLUBLE AGENTS

* * * * December 20, 2004

REPLY BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellant submits herewith a Reply Brief in triplicate in accordance with 37 C.F.R. § 1.193(b). This Reply Brief is timely filed within two months of and in response to the Examiner's Answer mailed October 20, 2004.

Appellant acknowledges the withdrawal of the rejections based on Davis and Kaufman under 35 U.S.C. § 102 individually. The only remaining rejections are over Davis and Kaufman under 35 U.S.C. § 103 individually. Appellant submits that the claimed invention is patentable over each of Davis or Kaufman for the many reasons advanced in his Appeal Brief. Appellant provides the following additional remarks in response the Examiner's Answer.

Appellant respectfully submits that all of the Examiner's rejections fail simply because the Examiner does not recognize that the present invention relates to "supersaturation" while the cited references only teach saturation up to the normal saturation limits (solubility limit). The solubility limit of compounds in water and other solvents is now very well known. By definition, the solubility limit of a specific compound (drug) is the absolute maximum amount of that compound that can be

dissolved in the solvent. Appellant has now found a novel method to go beyond this absolute solubility limit and provide novel supersaturated solutions that are stable.

Many drugs are so poorly soluble they must be administered with large volumes of carrier and/or with the use of toxicologically hazardous organic solvents. The present invention solves both of these serious problems by supersaturating poorly soluble drugs in an oil/aqueous carrier that is free of toxicologically hazardous organic solvents. By supersaturating the drug, significantly less carrier needs to be used to provide the same drug dose so that the drug can be safely injected into the human bloodstream. The Examiner fails to recognize these unexpected advantages and differences from the prior art. The Examiner's position in regards to Davis is "[t]here is no significant distinction observed between the prior art and the instant invention since the prior art teaches the applicant's claimed desired objectives of a dispersion comprising an oil-in-water emulsion administered intravenously." [See page 5, last paragraph of Examiner's Answer.] In regards to Kaufman, the Examiner similarly concludes "[t]he prior art teaches similar amounts using the same composition." [See page 8 of the Examiner's Answer.] These conclusions are simply wrong as shown in Appellant's Appeal Brief and for the following reasons.

Appellant will respond to each argument raised in the Examiner's Answer in the order provided by the Examiner. The Examiner first argues that:

Regarding the instantly claimed amounts, Davis *et al.* teach similar amounts and percentages as desired by the applicant. Furthermore, it would have been obvious to one of ordinary skill in the art that suitable amounts and percentages could be determined through the use of routine or manipulative experimentation. Additionally and in the absence of showing any criticality, the applicant has not shown any unexpected results that accrue from the use of the instantly claimed amounts. The prior art teaches suitable concentrations to arrive at stable emulsions. [(emphasis added) See page 6, second paragraph in Examiner's Answer.]

Appellant has on numerous occasions in his replies to Office Actions as well as in his Appeal Brief pointed out to the Examiner the unexpected advantages of the claimed invention, including (1) supersaturating the drug to reduce the amount of carrier

necessary and (2) avoidance of toxicologically hazardous organic solvents. The Examiner simply refuses to acknowledge these advantages. Furthermore, the Examiner has not cited any teachings or even a suggestion in any of the cited references as to how one prepares a stable supersaturated solution. Supersaturation cannot be equated with normal solubility limits. They are directly opposed, since either the drug is present at normal solubility limits or it is present at greater than normal solubility limits.

Furthermore, there was found a very unexpected result in the process itself. In the case of poorly soluble drugs such as amphotericin B it is not possible to dissolve drug crystals in an emulsion just by adding the drug powder to the emulsion. The low saturation solubility in water leads to an extremely low dissolution velocity, thus even shaking of an emulsion over days will not completely dissolve the drug powder. Of course, for preparing a pharmaceutical product such a process cannot be applied. There is the alternative to make an ultrafine precipitate by adding amphotericin B as a solubilised solution, that means injecting the commercial product Fungizone® into a bottle of parenteral fat emulsion (e. g. Intralipid). Even when doing this, it could be shown that even shaking for 18 hours at 2800 rounds per minute was not able to completely dissolve the finely precipitated amphotericin B (reference: Shadkhan et al., The use of commercially available lipid emulsions for the preparation of amphotericin B-lipid admixtures, *J. Antimicrob. Chemother.* 39, 655-658, 1997). Even when storing the shaken emulsions for another month, only 90% of the amphotericin B were associated with the droplets, and 10% still remained undissolved. In contrast to this it was very surprising that co-homogenisation of even a very coarse powder added to an emulsion led to complete dissolution of amphotericin B in relevant therapeutic concentrations (even within a few homogenisation cycles) which is not achieved by prior art.

The Examiner then argues that:

Kaufman et al. teach stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water (see abstract). There is no significant distinction observed between the prior art and the instant

invention since the prior art teaches the applicant's claimed desired objectives of a dispersion comprising an oil-in-water emulsion administered intravenously.

Furthermore, the applicant has not demonstrated any unexpected results that accrue from the instantly claimed percentages or ranges. The prior art teaches similar amounts using the same composition.

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Kaufman *et al.*, who teach an oil-in-water emulsion administered for intravenous administration, comprising a poorly soluble drug (taxol) because, Kaufman *et al.* teach that such a composition would exhibit minimal side effects and successfully overcome the previous deficiencies of the prior art. The expected result would be a stabilized oil-in-water emulsion for administering taxol intravenously. [(emphasis added) Page 8 in Examiner's Answer.]

Once again the Examiner simply ignores the distinction between supersaturation and well-known solubility limits. Supersaturation in combination with stability (shelf life) is a huge advantage over the prior art. The present invention can administer a poorly soluble drug using far less carrier and without toxicologically dangerous organic solvents. In contrast, the prior art must use far greater amounts of carrier and/or organic solvents. These are significant advantages that the Examiner simply ignores.

Since the Examiner does not explain how the amounts are "similar" or how to make a supersaturated composition, Appellant submits that the Examiner has not met his burden to show how the claimed invention is obvious from cited references.

The Examiner argues that:

Appellant urges the claimed invention is not taught or suggested by Davis ('845). Appellant urges, "It is surprisingly possible to enter the supersaturated concentration range without precipitation of drug crystals during storage. This is achieved by novel production technology discovered and disclosed in the present application, for example, co-homogenization of drug powder and oil in water. In contrast, it is well known throughout the art, that supersaturation of drugs in a carrier provides an unstable composition in which the drug crystallizes out of solution over time. The cited references are in agreement with this by only teaching to use compositions containing drugs at their solubility limit."

The Examiner has not been persuaded by this argument. "[E]ven though product-by-process claims are limited by and defined by the

process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). See also *In re Marosi*, 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983). In the instant case, the prior art teaches similar dispersion compositions comprising similar components as that desired by the instant invention. [See page 10 of Examiner's Answer.]

The Examiner's argument is without merit, for the simple fact that, not only are the methods different, but the product of the claimed invention and the product of the prior art are also very different. The claimed product has the drug in a stable "supersaturated" form, whereas the prior art product only has the drug dissolved up to normal solubility limits.

Furthermore, while the Examiner is correct that both systems are using an oil, water and lecithin with a drug added, the composition by Davis contains additionally organic solvent residues. These solvent residues are specifically avoided by the claimed process and are not present in the claimed product.

The Examiner then argues:

Appellant urges, "At supersaturation levels, the claimed invention is able to provide a dose containing far less carrier than the prior art compositions. Thus, any undesirable effects due to the carrier are substantially reduced in the present invention."

The Examiner has not been persuaded by this argument since the instant claims do not recite any particular amount of carrier in the formulation. [See page 11 of Examiner's Answer.]

The instant claims do in fact recite a particular amount of carrier in the formulation, less than the prior art compositions by definition. If the claimed composition has the drug at a supersaturated amount in the carrier, for the same drug dose, the prior art composition must by definition have a greater amount of carrier since the drug is only present up to normal solubility levels.

Of course, no specific percentage range can be given for drugs to be incorporated. The saturation solubility of each drug in the oil and water phase of the emulsion is different. However, the solubility limit can be exactly determined without undue experimentation for each selected drug and each water and each oil phase, or simply looked up in the literature as solubility limits are now very well known.

For example, the drug can be added to an oil phase and shaken until a maximum dissolved drug concentration is reached in the simultaneous presence of still non-dissolved drug crystals, which is the definition of the saturation solubility. Therefore, specifying in claim 1 that the drug concentration is above of the sum of the saturation solubilities is very precise because saturation solubilities are clearly defined.

The term supersaturation is also clearly defined. It is a dissolved drug concentration above the saturation solubility c_s . Such a supersaturated system can be created under certain experimental conditions, but it is thermodynamically highly unstable. For example, such a supersaturated system can be achieved by transferring a crystalline drug powder to the amorphous state and dissolving the amorphous powder. According to the Ostwald-Freundlich equation a supersaturated system is created. However, this is highly unstable leading to the precipitation of drug in form of normal crystals, this effect is qualitatively described in the so-called Ostwald-Mier diagram.

Based on this physical framework it was completely unexpected that a supersaturated state could be maintained (stabilized) after incorporation of drugs in a supersaturated concentration in the present invented compositions.

The Examiner argues:

Next, Appellant urges, "The claimed invention does not contain any organic solvents. In contrast, the cited prior art contains organic solvents. Even the 'minimal side effects' caused by the organic solvents alluded by the Examiner are completely avoided by the present invention."

These arguments were not found persuasive. The Examiner notes that the instant claims utilize "comprising" claim language and thus permit the inclusion of additional unrecited elements, such as organic solvents. Moreover, one of ordinary skill familiar with this art would be fully capable of determining suitable solvents, which do not provide for adverse effects,

but only positive effects, based on the desired or intended purpose at hand. The prior art ingredients allow for stable emulsions and thus would not be deemed detrimental to the formulation itself. [(emphasis added) See page 11 of Examiner's Answer.]

The Examiner attempts to rewrite over 100 years of patent law with his argument that the term "comprising" now trumps all other claim language such that claim limitations can simply be ignored. Appellant's claim 1 specifically recites "the dispersion is free from toxicologically dangerous organic solvents." This claim limitation is clear on its face and yet the Examiner simply refuses to consider it.

The Examiner's conclusion that organic solvents are "unrecited elements" is simply wrong. As stated previous, Appellant specifically excludes toxicologically dangerous organic solvents.

The Examiner's argument that those of ordinary skill in the art would be "fully capable of determining suitable solvents" is irrelevant. Those of ordinary skill in the art prefer no organic solvents in present in drugs that are injected into the human bloodstream because they cause undesirable effects. However, since many drugs are poorly soluble in an aqueous solution, they are forced to use such organic solvents. The present invention solves this problem and avoids the use of such organic solvents.

Even when using alcohols such as methanol (Davis), these alcohols are toxic. The Examiner has argued that an alcohol such as ethanol is not necessarily toxic. However, there are patients, previous alcohol addicts, who are not allowed to take any ethanol-based medicines, e.g. such as alcoholic extracts. Therefore, even ethanol needs to be removed from drug formulations. There is an increasing awareness about ethanol in pharmaceutical products. All of these problems are avoided by the present invention.

The Examiner argues:

Appellant urges, "Davis teaches clear limits to the drug concentrations, i.e., the solubility of the drug. For example, Davis discloses up to 1 mg/ml, preferably 0.5 mg/ml of Amphotericin (col. 4, lines 14-16). Davis only teaches to dissolve the drug in amounts up to the saturation concentration of the drug in the oil and water."

The Examiner has not been persuaded by this argument. Davis does not teach 'clear limits' as urged by the Appellant, but rather, Davis teaches that the "level of drug may be chosen by one skilled in the art to suit the dosage regimen and so on but may *typically* be up to 1 mg/ml" (see cot. 4, lines 14-16). The term "typically" is an equivalent and suggested term, which is not deemed to be limiting in any manner. The art teaches a suggested amount that does not set any particular limits. [(emphasis in original) See page 11 of Examiner's Answer.]

The Examiner's interpretation of the term "typically" to now be all encompassing is absurd. The term typical is used to denote, for example, a well known property or trait that is common among a class. One would not use the term typical to mean a new, heretofore, unknown property or trait. A "typical" concentration in the cited references is that which is well known, i.e. the solubility limit. It is not typical to go beyond what is perceived as the limit throughout the art.

The Examiner states:

Next, Appellant urges, "A main difference overlooked by the Examiner is the achieved drug loading: (1) the saturation concentration with Davis and Kaufman; and (2) in the supersaturation range in the present invention. In the present invention, going beyond the saturation limit and even doubling the saturation solubility is unexpected and something which is not predictable from Davis. Davis does not teach supersaturation of drugs."

These arguments were not found to be persuasive. The prior art desires "reduced toxicity" of the drug, as desired by Appellant (see Davis Abstract). No unexpected results are observed from the increased drug amounts, as urged by Appellant. [(emphasis added) See page 12 of Examiner's Answer.]

Appellant's invention is not merely "increased drug amounts," rather increased concentration of the drug. If the concentration of the drug is increased, less carrier is needed to deliver the drug. Appellant stresses that going beyond the saturation limit, supersaturation, means that for a given drug dose, the amount of carrier will be substantially reduced compared to the amount of carrier required in the cited references. For example, for poorly soluble drugs the administration volume is in most cases relatively large, e.g. requiring an infusion of 100-500 ml of emulsion carrier. It is

a distinct advantage when the same amount of drug can be administered in form of an injection, that means e.g. a volume of 10 ml emulsion carrier.

The Examiner states:

Appellant urges, "The Examiner is not correct in stating that the prior art teaches suitable concentrations to arrive at stable emulsions. The prior art concentrations are not sufficiently high to obtain acceptable injection volumes. The previous emulsions are even below the saturation concentration, i.e., they are not supersaturated emulsions. The emulsions of the invention are also stable, but the key feature is the supersaturation, which provides suitable injection volumes."

The Examiner has not been persuaded by this argument. The Appellants have not demonstrated that the concentrations taught by the prior art are not suitable or effective concentrations. Moreover, the prior art teaches and achieves the same objectives as instantly desired by Appellants, which is to provide "stable" drug emulsions. See Abstract of Davis, wherein Davis states that the emulsions are stable and reduce the toxicity of the drug. [(emphasis added) See page 12 of Examiner's Answer]

The Examiner simply ignores the "suitable injection volumes" argument presented by Applicant and instead refers to stability. Stability and injection volume are two distinctly different properties. Of course Davis will provide a stable composition, since he is only dissolving the drug up to its normal solubility limit. However, Davis does not teach or even suggest in the slightest how make a stable composition where the drug is dissolved at greater than its normal solubility limit.

While an emulsion according to Davis or Kaufman can be administered to the patient, in general this is very inconvenient and uncomfortable for patients because of the large volume of carrier required, as discussed above. In addition it needs to be considered that the emulsions are used for parenteral nutrition. When only administered as a carrier for a drug, the nutritional load is desired to be minimised to avoid interference with the patients normal nutrition. The claimed invention provides the advantage of significantly reducing the amount of emulsion carrier necessary to provide the same drug dose.

The Examiner argues that:

With respect to Kaufman *et al.*, the Appellant urges, "In the present invention, all side effects due to the organic solvents are avoided since no organic solvents are present. The prior art does not teach or suggest avoiding all side effects by using a composition containing no organic solvents."

These arguments were not found to be persuasive. A review of Applicant's specification at page 9, lines 6-9 indicates that 'for stabilization of the dispersions, emulsifiers and stabilizers can be used. These are possibly already contained in the emulsion used to produce the dispersion according to the invention, addition of further emulsifiers and stabilizers can be advantageous in the production of the dispersion'. Various emulsifiers, such as surfactants are also listed at page 9, lines 11-23. The arguments were not persuasive since the scope of the instant claims does not address the scope of Applicant's invention. Emulsifiers, surfactants and stabilizers are all permitted by the scope of the instant claims. Typical concentrations are 0.1-20% (see pg. 9, line 22). Thus, the argument that 'no organic solvents are present' is not persuasive. [(emphasis added) See page 13 of Examiner's Answer.]

Appellant simply does not understand the Examiner's logic of comparing emulsifiers and surfactants to organic solvents. Appellant's claims specifically recite "free from toxicologically dangerous organic solvents." Appellant requested that the Examiner consider this claim limitation and not some other claim limitation relating to emulsifiers and surfactants.

The Examiner states:

Lastly, Appellant urges, "Davis and Kaufman do not disclose that the active drug can be present in solid crystalline form as recited in claim 2. Davis and Kaufman both require that the drug be dissolved, which is in a direction opposite to that of solid drug crystals. Davis and Kaufman do not teach how to make a dispersion containing the active ingredient dissolved in quantities greater than a factor of 1 (normal solubility) and cannot make obvious a supersaturation at a factor of 2, 5 and 10 times the normal solubility. Claims 149-150 recite the language 'organic solvent-free' and the Examiner has not made a *prima facie* case of obviousness."

These arguments were not found to be persuasive. Applicant's claims do not require the subsequent dispersion of the oil-in-water emulsion or a water-in-oil emulsion subsequently in water. The specification teaches this procedure at page 10, lines 26-36, but the instant claims do not require that. If Applicant has a dispersion in the

presence of emulsifiers, stabilizers and surfactants, it is the position of the Examiner, that absent a direct comparison of the prior art, renders the instant dispersions obvious. There is no distinction between the dispersions being claimed and those in the art, other than the degree of the dissolved active ingredient. Applicant's desired properties are a) stability and b) reduced toxicity. The prior art's desired properties are also stability and reduced toxicity. The described differences are of degree and not of kind. The prior art clearly recognizes Applicant's desired properties. Hence, no unexpected results are seen in the 'supersaturated' dispersions as recited in the claims that would *patentably* define over the cited references. Thus, the Examiner believes that the instant invention is rendered *prima facie* obvious over the prior art of record. [(emphasis in original) See pages 13-14 of Examiner's Answer.]

Appellant stresses that the Examiner has not shown how the cited references teach the claim limitation "the active drug can be present in solid crystalline form." For this simple reason, the Examiner not met his burden of providing a *prima facie* case of obviousness. Furthermore, Appellant submits that they do not have a burden to compare the claimed products with those of the cited references, especially when the cited references do not even teach any products having the drug in solid crystalline form.

Davis and Kaufman teach completely different processes to make different products than those of the claimed invention for the many reasons provided in Appellant's Appeal Brief and for the following reasons.

Davis dissolves the drug and lecithin in an organic solvent, evaporates the solvent and use this mixture for emulsion production. Thus, Davis' final product contains organic solvent residues. In contrast, Appellant's process does not need any organic solvents and, thus, the claimed product does not contain these residues. This is advantageous, because it is a costly process to remove the solvents, firstly to remove the solvent itself and secondly – in case of production of sterile parenteral products – the additional costs to remove the solvent under aseptic conditions. Therefore, the presently claimed process has distinct advantages over Davis.

Even when using alcohols such as methanol (Davis), these alcohols are toxic. The Examiner has argued that an alcohol such as ethanol is not necessarily toxic. However, there are patients, previous alcohol addicts, who are not allowed to take any ethanol-based medicines, e.g. such as alcoholic extracts. Therefore, even ethanol needs to be removed from drug formulations. There is an increasing awareness about ethanol in pharmaceutical products. At the moment we are seeing the replacement of ethanolic plant extracts with aqueous plant extracts, just because of this awareness and the ethanol problem.

Kaufman also is very different from the claimed invention. Kaufman incorporates the drug by solubilising it in the oil phase. It is based on the fact that the drug is basically soluble in oil, therefore Kaufman et al. prefers e.g. safflower oil compared to soybean oil. The present invention is very different in that the drug does not have to be dissolved in the oil phase (Kaufman). In the present invention, poorly oil soluble drugs can be incorporation into the emulsion by localising the drug into the interfacial layer between oil and water. Even when using a drug that has a certain solubility in the oil, the overall amount of drug incorporated in the present invented emulsion is higher than the amount resulting from the solubility in the oil and the water phase. That means the presently claimed emulsions are characterised that drugs can be incorporated at a concentration above the amount from the saturation solubilities in the water and the oil phase.

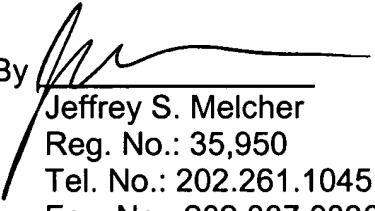
This is also reflected in present claim 1 by characterising the emulsion composition such the drug concentration in the emulsion is higher than based on its saturation solubilities in the water and the oil phase. All the other emulsion systems described in the cited references contain drugs in concentrations only up to the total of the maximum solubility in the two phases. Therefore, the concentration of drug the present invention is clearly differentiated from the cited prior art emulsions.

Conclusion

For all of the reasons advanced in Appellant's Brief On Appeal and for the reasons advanced above, it is submitted that the present invention as recited in each of Appellant's claims is in proper condition for allowance. Accordingly, Appellants respectfully request that the Board allow claims 1-15, 19-66, 143, 146 and 148-150 over the cited references.

Respectfully submitted,

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